

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Luba COHEN.
Serial Number: 09/955,933
Filed: September 20, 2001
For: LICORICE EXTRACT FOR USE AS A MEDICAMENT
Art Unit: 1651
Examiner: Deborah K. Ware

DECLARATION OF MICHAEL AVIRAM UNDER USC 37 §1.132

Mail Stop AF
Honorable Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:


I, the undersigned, Michael AVIRAM, a citizen of Israel, whose address is, The Lipid Research Laboratory, Rambam Medical Center, Bat Galim, Haifa, Israel 31096 , do solemnly declare, as follows:

1. I was named as co-author in an article titled "Licorice extract and its major polyphenol glabridin protect low-density lipoprotein against lipid peroxidation: in vitro and ex vivo studies in humans and in atherosclerotic apolipoprotein E-deficient mice" published in American Journal of Clinical Nutrition volume 66 (1997) pages 267-275 by the American Society for Clinical Nutrition (hereinafter Fuhrman et al).
2. My curriculum vitae is attached herewith as part of this declaration.
3. The scientific work described in Fuhrman et al was done under my supervision.
4. Fuhrman et al describes that an ethanolic extract of licorice reduced LDL susceptibility to oxidation, and reduced atherosclerotic lesion in atherosclerotic mice.
5. Fuhrman et al describes that the same ethanolic extract of licorice had no significant effect on blood cholesterol levels in healthy humans.
6. The component identified in Fuhrman et al to be active as an anti-oxidant was glabridin.
7. The chemical structure of glabridin does not resemble that of anti-hypercholesterolemic drugs known to me, neither does it resemble the chemical structure of anti-hypertension drugs known to me.

8. Fuhrman et al does not describe, and I am not aware of any scientific article that did describe, prior to the date of the application, any other constituent of ethanolic licorice extract, the chemical structure of which does resemble that of any of the above-mentioned drugs.
9. I was surprised to find, in performing another research, in hypercholesterolemic patients, conducted under my supervision, that ethanolic licorice extract is in fact effective to reduce systolic blood pressure. I was also surprised to find, in the same research, that ethanolic licorice extract reduces plasma lipid levels.
10. The findings mentioned under paragraph 9 above were published on 2002 in Nutrition, 18:268-273, under the title "atniatherosclerotic effects of licorice extract supplementation on hypercholesterolemic patients: increased resistance of LDL to atherogenic modification, reduced plasma lipid levels, and decreased systolic blood pressure".

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true

December 24 2006
Date


Michael AVIRAM



TECHNION – FACULTY OF MEDICINE

Date: November 2006

RESUME

1. PERSONAL DETAILS

MICHAEL AVIRAM

**Professor, Head of the Lipid Research Laboratory, Technion Faculty of Medicine, Rappaport
Institute for Research in the Medical Sciences and Rambam Medical Center, Haifa, Israel**

<http://hebrew.rambam.org.il/aviram>

<http://www.technion.ac.il/~medicine/faculty/lipid.htm>

<http://www.technion.ac.il/~rapinst/aviram.html>

http://md.technion.ac.il/inner/department.php?department_id=50

Date & Place of Birth: December 7, 1948, Israel. (ID # 00557978-4)

Marital status: Married to Bruria, 3 children (Amitai, Yotvat and Rohtem).

Work Address: Lipid Research Laboratory, Technion Faculty of Medicine,
and Rambam Medical Center, Haifa, Israel 31096

Tel: 972-4-8542970 Fax: 972-4-8542130 E mail: aviram@tx.technion.ac.il

Home address: 59 Haplugot St., Kiriath-Haim, 26253, Israel. (Tel: 972-4-8704587).

2. ACADEMIC DEGREES

1975-1978 **Doctorat Studies**, Clinical Biochemistry, Faculty of Medicine, Technion - Israel
Institute of Technology, Haifa, Israel.

D.Sc. (Supervisor: Nobel Prize Laureate Prof. Avram Hershko).

1973-1975 **Graduate Studies**, Clinical Biochemistry, Faculty of Medicine, Technion -Israel,
Institute of Technology, Haifa, Israel.

M.Sc. (Supervisor: Nobel Prize Laureate Prof. Avram Hershko).

1966-1970 **Undergraduate Studies**, Chemistry, Technion-Israel Institute of Technology,
Haifa, Israel, **B.Sc.**

* Israel Defence Forces (1970-1973, final rank in Reserve – Lieutenant Colonel)

1978- 1980 **Postdoctoral Fellow:** Arteriosclerosis Center, Massachusetts Institute of
Technology (M.I.T), Cambridge, MA, U.S.A.

3. ACADEMIC APPOINTMENTS

- 2004 – present **Professor of Biochemistry**, Technion Faculty of Medicine, Haifa, Israel
- 1991- 2004 **Associate Professor of Biochemistry**, Technion Faculty of Medicine, Haifa, Israel.
- 1997-1998 **Professor (Visiting)**, University of Michigan, Ann Arbor, MI, U.S.A.
 "Paraoxonase, lipid peroxidation, and macrophage cholesterol accumulation: molecular and cellular biology" (with Prof. Bert La Du).
- 1991-present **Member**, The Rappaport Institute for Research in the Medical Sciences, Haifa, Israel.
- 1994-2000 **Deputy Director**, The Rappaport Institute for Research in the Medical Sciences, Haifa, Israel.
- 1987-1988 **Associate Professor (Visiting)**, Division of Metabolism, Department of Medicine, University of Washington, Seattle, WA, U.S.A. "Lipase-modified LDL and macrophage cholesterol metabolism" (with Prof. Edwin Bierman and Prof. Alan Chait).
- 1986-1987 **Visiting Scientist**, Specialized Center of Research (SCOR) in Atherosclerosis, Department of Medicine, Columbia University, New York, NY, U.S.A. "Lipoprotein lipids modifications and macrophage cholesterol accumulation". (with Prof. Richard Deckelbaum).
- 1989-1997 **Adjunct Associate Professor**, Department of Food Engineering and Biotechnology, Technion, Haifa, Israel.
- 1985-1989 **Adjunct Assistant Professor**, Department of Food Engineering and Biotechnology, Technion, Haifa, Israel.
- 1984 **Visiting Scientist**, Institute of Clinical Medicine, University of Tromso, Tromso, Norway (3 months) "Dietary fatty acids, lipoproteins, and endothelial cell function". (with Prof. Arne Nordoy).
- 1983 **Visiting Scientist**, Institute of Pharmacology, University of Milano, Milano, Italy. "Plasma lipoproteins and platelet prostaglandins". (with Prof. Cesare Sirtori).
- 1973-1978 **Instructor**, Clinical Biochemistry, Faculty of Medicine Technion - Israel Institute of Technology, Haifa, Israel.

- 1975-1978 **Doctoral Studies**, "Turnover of the enzyme tyrosine-aminotransferase".
Clinical Biochemistry, Faculty of Medicine, Technion-Israel Institute of
Technology, Haifa, Israel. (Supervisor: Nobel Prize Laureate Prof. Avram
Hershko).
- 1973-1975 **Graduate Studies**, "Degradation of RNA in cultured hepatoma cells".
Clinical Biochemistry, Faculty of Medicine, Technion - Israel Institute of
Technology, Haifa, Israel. (Supervisor: Nobel Prize Laureate Prof. Avram
Hershko).
- 1966-1970 **Undergraduate Studies**, Faculty of Chemistry, Technion - Israel Institute of
Technology, Haifa, Israel.

4. PROFESSIONAL EXPERIENCE AND DUTIES

Technion and Rambam Medical Center Activities

- 1980-present Head, Lipid Research Laboratory, Technion Faculty of Medicine, Rappaport
Institute for Research in the Medical Sciences, and Rambam Medical Center.
- 1999-present Chairman, Department of Laboratory Medicine, Rambam Medical Center.
- 2006 Member of the Technion's Senate Harvey Prize Committee.
- 2005-present Member of the Technion's Senate Standing Committee and the Elected Senate.
- 2005-present Member of the Technion Academic Council for Continuous and External Studies.
- 2004-present Member of the Technion's Senate Committee for Research.
- 1994-2005 Chief Scientific Advisor, Rambam Medical Center.
- 1993-2001 Member, Committee for Human Resources, Rambam Medical Center.
- 1994-2000 Deputy Director, Rappaport Institute for Research in the Medical Sciences.
- 1994-1997 Head, Committee for Teaching and Curriculum, Technion Faculty of Medicine.
- 1993-1996 Chairman, The Technion Committee for Promotion of Laboratory Technicians.
- 1994-1996 Member, Committee for Graduate Studies, Technion Faculty of Medicine.
- 1993-1994 Deputy Head, Committee for Research, Technion Faculty of Medicine.
- 1993-1994 Deputy Head, Committee for Teaching, Technion Faculty of Medicine.
- 1991-1994 Member, the Secretariat, Board of Medical Research, Israel Ministry of Health.

International and National Activities

- 2004-2007 Member of the Scientific Advisory Board and of the Executive Board of Governors ,
D- CURE, a non-profit Diabetes Research Organization.
- 2006 Chairman, Israel Science Foundation (ISF) Centers of Excellence Committee.
- 2004-present Member, the Editorial Advisory Board, *Drug Design Reviews – Online*.
- 2004-present Member, the Editorial Board, *Medicinal Chemistry Reviews*.
- 2004-present Member, the Editorial Board, *Israel Medical Association Journal*.
- 2004-2005 Guest Editor for the Peroxisomes Serial Reviews: Free Radical Biology & Medicine.

- 2002-2005 Member, Committee of Process for the assessment of Scientific support for Claims on Food (PASSCLAIM, Group on Diet related atherosclerosis).
- 2001-2002 Member, the Ministry of Health Committee for Continuous Education Reward (Gemul Hishtalmut).
- 2001-2005 Member, the Scientific Advisory Board, Lycopin Fourm. Germany
- 2000-2005 Scientific Advisor, Roche Diagnostics GmbH, Penzberg, Germany.
- 2000-2005 Member, the Scientific Advisory Board (SAB), Molecutec and PharmaVitae, Molecular Technology Corporation, New York, NY, USA.
- 2000-2005 Member, the Scientific Advisory Board (SAB), Esperion Therapeutics, Ann Arbor, MI, USA.
- 2000-2005 Member, the Scientific Advisory Board (SAB), BioPreventive, Noninvasive Biomedical Diagnostic Tools, Migdal-Haemek, Israel.
- 2000-2005 Member, the Scientific Advisory Board (SAB), Profile Advanced Technologies (PAT), Jerusalem, Israel.
- 2000-present Member, the Editorial Board, *Current Medicinal Chemistry*.
- 1998-present Member, the Scientific Advisory Board (SAB) ROLL International, PomWonderful, LA, CA, USA.
- 1996-present Member, the Editorial Board, *Czynniki Rzyzyka*.
- 1985-1989 Editor-in-Chief, Israel Journal of Clinical Biochemistry and Laboratory Sciences.
- 1981-1993 Member, the Secretariat, Israel Society for Clinical Biochemistry (ISCB).
- 1981-1986 Member, the Secretariat, Israel Biochemical and Microbiological Union (IBMU).
- 1980-1986 Member, the Secretariat, Israel Biochemical Society (IBS).
- 1970-1973 Israel Defence Forces. Final rank in reserves – Colonel.

* REVIEWER FOR ALL MAJOR INTERNATIONAL JOURNALS ON ATHEROSCLEROSIS.

5. RESEARCH INTERESTS

General Goal: Study of Mechanisms involved in Macrophage Cholesterol accumulation and Foam Cell formation under Oxidative Stress during Atherogenesis: Role of Dietary Antioxidants and of Paraoxonases.

Specific Areas of Research:

1. Lipoproteins Oxidation and Atherosclerosis (1980 – present)

Macrophage – mediated oxidation of LDL and foam cell formation are the hallmark of early atherogenesis. We were the first to demonstrate the role of cellular oxygenases (such as NADPH oxidase) and of antioxidants (such as the glutathione system) in cell - mediated LDL oxidation and in atherosclerotic lesion development.

2. Dietary Antioxidants and Atherosclerosis (1990 – present)

We have provided evidence, for the first time, that the inhibitory effect of some flavonoid antioxidants on macrophage – mediated LDL oxidation (and on atherosclerosis development) is related to the polyphenols interaction with the lipoprotein directly, as well as to their accumulation in arterial macrophages.

3. Paraoxonases, Lipid Peroxidation and Atherosclerosis (1997 – present)

Recently, we provided evidence that HDL- associated Paraoxonase can hydrolyze oxidized lipids in oxidized lipoproteins, macrophages, and in atherosclerotic lesions. Paraoxonase thus may act as a second line of defense against oxidative stress and atherosclerosis development.

6. TEACHING EXPERIENCE

1992-present

Chairing and teaching **basic courses** to Medical Students.

1. Chair and lecturer: **Biochemistry** to Medical Students (Course # 274226).
2. Chair: **Biochemistry Laboratory** (Course # 274227).
3. Lecturer: **Clinical Biochemistry** to Medical Students (Course # 276310).

1981-present

Chairing and teaching in **elective courses** to Medical and Graduate Students:

1. **Lipoproteins and Atherosclerosis** (Course # 277426).
 2. **Lipids and Lipoprotein Metabolism** (Course # 068318).
- * Teaching: **Clinical Biochemistry** to undergraduate students, Faculty of Life Sciences, Bar Ilan University, Ramat-Gan, Israel (1992-1999).

2002-present - Technion Permanent Outstanding Lecturer

Outstanding teacher, Faculty of Medicine: every year since 1993

- 2001 - Faculty of Medicine, Outstanding Lecturer. Score – 4.76 (out of 5.00).
- 2000 - Muriel and David Jacknow Award for Excellence in Teaching.
- 2000 - Faculty of Medicine, Outstanding Lecturer. Score – 4.71.
- 1999 - Faculty of Medicine, Outstanding Lecturer. Score - 4.76.
- 1997 - Faculty of Medicine, Outstanding Lecturer. Score - 4.64.
- 1996 - Faculty of Medicine, Outstanding Lecturer. Score - 4.70.
- 1995 - Faculty of Medicine, Outstanding Lecturer. Score - 4.67.
- 1994 - Faculty of Medicine, Outstanding Lecturer. Score - 4.64.
- 1993 - Faculty of Medicine, Outstanding Lecturer. Score - 4.70.
- 1993 - Technion President Award : Best Lecturer of the Year.

7. MEMBERSHIP IN PROFESSIONAL SOCIETIES

National

- Israel Society for Atherosclerosis.
- Israel Society for Diabetes.
- Israel Society for Laboratory Medicine (previously - Clinical Biochemistry).
- Israel Biochemical Society.
- Israel Society for Oxygen and Free Radical Research.

International

American Society for Biochemistry and Molecular Biology (ASBMB).
 Academy of Clinical Laboratory, Physicians and Scientists.
 American Heart Association. Council on Arteriosclerosis.
 American Association for Clinical Chemistry.
 American Federation for Clinical Research.
 Biochemical Society.
 European Society for Clinical Investigation.
 European Atherosclerosis Society.
 European Lipoprotein Club.
 International Atherosclerosis Society.
 International Society for the study of Fatty acids and Lipids (ISSFAL).
 International Society for Free Radical Research (ISFRR).
 International Society on Thrombosis and Haemostasis.

8. HONORS

2002 - Technion Permanent Outstanding Lecturer Award

Outstanding teacher, Faculty of Medicine every year since 1993

1998 - Pfizer Lecturer Award, Clinical Research Institute of Montreal, Canada
 ("LDL oxidation and atherosclerosis").

1998 - NIH, Office of Alternative Medicine (OAM),Symposium Award
 ("Antioxidants, LDL oxidation and atherosclerosis").

1994 - Senior Investigator International Prize for Research on Oxidation of
 Lipoproteins: The ARCOL Prize, Pastuer Institute, Lille, France
 ("Macrophage-mediated oxidation of LDL").

1994 - Faculty of Medicine Award for Scientific achievements.

1993 - Faculty of Medicine Award for scientific achievements.

1993 - Servier Investigator Award for Research on Antioxidants. European
 Society on Free Radicals Research, Valencia, Spain.

1987 - Fogarty International Fellowship (Seattle, WA, USA). "Lipids-modified LDL".

9. STUDENTS INSTRUCTION

D.Sc. / Ph. D. Theses

1. Bianca Fuhrman: "Platelet secretory products and macrophage lipoprotein metabolism". 1988-1992.
2. Melia Paizi: "The possible role of fibronectin in plasma cell dyscrasia related problems." 1986-1990 (Co- supervisor with Prof. G. Spira).
3. Qianmei Li: "Macrophage metabolism of the fatty acids in the LDL cholesteryl ester". 1993-1995.
4. Paula Belinky: "Licorice as an inhibitor of LDL oxidation". 1994-1998.
5. Irit Maor: "Relationships between oxidation and aggregation processes in LDL

- derived from apolipoprotein E-deficient mice during atherogenesis". 1995-1999.
6. Marielle Kaplan: "Proteoglycans and macrophage uptake of oxidized LDL" 1996-2000.
7. Andrea Szuchman: "Chemical markers for oxidative stress in biological systems". 2001-2005.
8. Orit Rosenberg (Grunfeld): "Paraonase 1 overexpression and protection against atherosclerosis" 2003-2006.
9. Maayan Sheiner (Ben-dor): "Paraonase 2 regulation in macrophages: signal transduction and transcription factor pathways" 2004-2007.
10. Hagai Tavori : "Paraonase protection against oxidative stress". 2007-2010.

M.Sc. Theses

1. Yaakov Berkovitz: "Platelet adhesion in whole blood". 1979-1981 (Co-supervisors: Profs Marmur and Brook).
2. Idit Bornstein: "Platelet adhesion". 1981-1983 (Co-supervisors: Profs Marmur and Brook).
3. Bianca Fuhrman: "The effect of chylomicrons on platelet function". 1983-1985 (Co-supervisor: Prof. Brook).
4. Nechama Segal: "Surfactants and platelet aggregation". 1984-1986 (Co-supervisors: Profs Marmur and Brook).
5. Edna Hochgraff: "The effect of lovastatin on platelet function, composition and fluidity in hypercholesterolemic patients". 1988-1990 (Co-supervisor: Prof. Cogan).
6. Irit Maor: "Platelet secretory products and macrophage cholesterol metabolism". 1990-1992.
7. Judith Oiknine: "The effect of macrophage activation on the uptake of LDL". 1991-1993.
8. Mira Rosenblat: "Macrophage oxidation of LDL". 1993-1995.
9. Limor Ben Yaish: "The effect of lycopene on macrophage cholesterol metabolism". 1995-1997.
10. Orit Grunfeld: "Paraonase and macrophage foam cell formation". 2000-2002.
11. Anat Katzir: "Oxidized LDL and macrophage MAP kinase signal transduction". 2000-2002 (Co-supervisor: Prof. Polack).
12. Maayan Ben-Dor: "Macrophage maturation and foam cell formation". 2002-2004.
13. Michal Efrat : "HDL phospholipids and paraonase 1 activities". 2006 – 2008.

Undergraduate Students

1. Nir Lubetchky - "Macrophage lipid peroxidation". 1992-1993.
2. Limor Ben Yaish - "Cell membrane lipid peroxidation in macrophages". 1994-1995.
3. Shlomi Buch - "Antioxidative properties of Licorice against LDL oxidation". 1994-1996.
4. Beha Francis - "Macrophage foam cell formation under oxidative stress". 1999-2000.
5. Ayelet Partush – " Acetyl Choline Esterase hydrolyzes lipid peroxides". 2004-2005.

6. Roni Oren – "LPC attenuates macrophage - mediated oxidation of LDL". 2005-2006.
7. Yasmin Chativ – "Macrophage paraoxonase 2 (PON2) regulation by the urokinase plasminogen activator (uPA) system". 2005-2006.
8. Orly Sapir – "Glucose destabilizes HDL – associated paraoxonase1 (PON1); implications to Diabetes". 2005-2006.

M.D. Theses

1. Ron Diukman: "The effect of soy protein diet on plasma lipoproteins in rabbits". 1977-1978.
2. David Ron: "HDL in the elderly". 1978-1979.
3. Ema Shilansky: "HDL in atherosclerotic patients". 1978-1979.
4. Michael Lanchet: "HDL in young males after myocardial infarction". 1979-1980.
5. Yitzchak Sarugo: "The effect of HDL on platelet function". 1980-1982.
6. Arthur Veschler: "The effect of carnitine on platelet function and plasma lipoproteins in patients with chronic renal failure on hemodialysis". 1980-1982.
7. Asher Shmulevitz: "Platelets LDL receptor". 1982-1983.
8. Eyal Herzog: "saturated fat rich diet on platelet function". 1982-1984.
9. Ron Hoffman: "Plasma lipoproteins in celiac disease". 1987-1988.
10. Elias Kasem: "Dietary olive oil and LDL oxidation in humans". 1991-1992.
11. Danniell Karter: "Macrophage-lipid peroxidation by PMA". 1994-1996.
12. Lena Koren: "Monocyte-macrophage differentiation under oxidative stress". 1999-2000.
13. Nir Shimoni : "High serum HDL and cardiovascular diseases". 2001-2002.
14. Ayelet Partush : "Oxidized LDL and macrophage foam cell formation". 2005-2006.
15. Rony Oren : "Lysophosphatidylcholine and macrophage –mediated oxidation of LDL". 2005-2006 .

Residents (Basic Science)

1. Gideon Derayfus- Carmel Hospital, Haifa: "The effect of dietary vegetarian proteins on plasma lipoproteins in rabbits". 1979-1980.
2. Ruth Baruch (Gershoni)- Rambam Hospital, Haifa: Plasma lipoprotein pattern in young children 1980-1981.
3. Jacob Baruch-Rambam Hospital, Haifa: Dyslipoproteinemia in primary biliary cirrhosis". 1980-1981.
4. Avi Viener-Rambam Hospital, Haifa: "The effect of plasma lipoproteins on platelet function in hypercholesterolemic patients". 1981-1982.
5. Giora Winterstein- Rambam Hospital, Haifa: "Prostaglandin pathway and platelet function in hypercholesterolemia". 1982-1983.
6. Nassara Chalil- Ziv Hospital, Zefat: "Plasma fatty acid after fat rich meal". 1983-1984.
7. Efrat Wolfovitz - Rambam Hospital, Haifa, "Macrophage lipid metabolism". 1984-1985.
8. Mondir Boulos - Rambam Hospital, Haifa: "The effect of plasma lipoproteins derived from hypercholesterolemic patients on macrophage cholesterol content". 1985-1986.

9. Lavi Klein-Rambam Hospital, Haifa: "Plasma lipoprotein fluidity in hypercholesterolemic patients". 1987-1988.
10. Ron Hoffman - Rambam Hospital, Haifa: "Anti oxidation properties of hypocholesterolemic drugs". 1990-1991.
11. Rafi Azugi - Ziv Hospital, Zefat: Effect of estrogen on plasma lipoprotein pattern. 1990-1991.
12. Osamah Hussein - Ziv Hospital, Zefat: "The effect of platelet secretory products on macrophage cholesterol metabolism in mouse peritoneum". 1990-1991.
13. Peter Barta - Rambam Hospital, Haifa: "Myocardial infarction and plasma lipid peroxidation". 1993-1994.
14. Yanir Kashif - Naharia Hospital, Naharia: "Xanthelasma and oxidized lipids". 1993-1994.
15. Sorina Schlesinger - Ziv Hospital, Zefat: "Fluvastatin and LDL oxidation". 1995-1996.
16. Gavriella Friedman-Ziv Hospital, Zefat: "Cholestyramine and LDL oxidation: 1995-1996.
17. Imad Sachnin: "Angiotensin II and macrophage cholesterol metabolism". 1998-1999.
18. Ayelet Raz - "Regression of atherosclerosis in apo E deficient mice by treatment with ACE inhibitors" - 1999-2000.
19. Shadi Hammood: "Effect of ACE inhibitors on oxidative stress and atherosclerosis in E⁰ mice". 2001-2002.
20. Chitani Hussein - "Paraoxonase 2 in macrophages from hypercholesterolemic patients; effect of statin therapy". 2003-2004.
21. Alex Strizevski - "Human monocyte-macrophage ACE2 expression in hypertensive patients" 2004-2005.
22. Ronen Saltz - "Macrophage atherogenicity in diabetes" 2004-2005.
23. Orna Nitzan - "Monocyte-macrophage differentiation under oxidative stress". 2005-2006.
24. Ido Bogner - "HDL composition affects its biological function and atherosclerosis". 2006-2007.

Collaborating Senior Physicians

1. Shlomo Keidar, M.D.: "Angiotensin II, LDL oxidation and atherosclerosis". Rambam Medical Center, Haifa, 1988 - present.
2. Tony Hayek, M.D.: "The atherosclerotic apolipoprotein E-knockout mice as a model to study lipoprotein modifications in atherosclerosis". Rambam Medical Center, Haifa, 1993 - present.
3. Osamah Hussein, M.D.: "Antioxidants against LDL oxidation and atherosclerosis". Ziv Hospital, Zefat, 1993 - present.
4. Raanan Shamir : "Intestinal paraoxonases". Rambam Medical Center, Haifa, 2001-2004.
5. Alexandra Lavy, M.D.: "Lipoprotein oxidation in atherosclerotic patients". Bnei Zion Hospital, Haifa, 1988 - 2000.
6. Yishai Levy, M.D.: "Carotenoids as antiatherogenic agents", Rambam Medical Center, Haifa, 1988 - 2000.
7. Avishay Elis, M.D.: "The effect of lycopene on macrophage cholesterol metabolism and atherosclerosis". Meir Medical Center, Kfar-Saba, 1996 - 2001.
8. Hanna Mandel, M.D.: "Peroxisomes and cholesterol metabolism" Rambam Medical Center, Haifa 1991-2000.

9. Reuven Bergman, M.D.: "Xanthelasma, Xanthogranulomatosis and cholesterol metabolism". Rambam Medical Center, Haifa, 1993 - 2000.
10. Daiana Gaitini, M.D. : Intima-Media Thickness (IMT) in atherosclerotic patients: effect of dietary antioxidants". Rambam Medical Center, Haifa, 2000-2004.

10. RESEARCH GRANTS

Academic

- | | |
|-----------|--|
| 2005-2008 | Rappaport Institute Research Grant - " Paraoxonases (PONs), Oxidized lipids and foam cell formation". - \$60,000 |
| 2005-2007 | Israel Ministry of Science and Technology – “Metabolic networks in pomegranate fruit: an analytical platform for food functionality” - \$200,000 (together with Holland D., Neve Yaar Research Center and Amir R., MIGAL Research Center). |
| 2004-2007 | The Israel Science Foundation (ISF, The Israel Academy of Sciences and Humanities) – “The search for endogenous substrates of paraoxonase” - \$90,000 (together with Dr J. Vaya., MIGAL Research Center). |
| 2004-2006 | D-Cure Diabetes Research Grant -“Paraoxonase (PON) substrates metabolic pathways under oxidative stress: studies under the diatetic environment” - \$130,000 (together with Dr J. Vaya., MIGAL Research Center). |
| 2004-2006 | The Niedersachsische Ministeriums fur Wissenschaft and Kultur - “Regulation of urokinase plasminogen activator (uPA) expression in monocytes during their differentiation into macrophages: consequences on atherogenesis in relation to macrophage-foam cell formation and to vascular smooth muscle cells migration and proliferation”. – EU 100,000. |
| 2005-2006 | Israel Ministry of Health – “Paraoxonase in hypercholesterolemic patients” – \$20,000. |
| 2004-2007 | The Israel Science Foundation (ISF, The Israel Academy of Sciences and Humanities) – “Regulation of macrophage atherogenicity by the haptoglobin polymorphism”. - \$200,000 (Cooperating Investigator. PI - Dr. A. Levy). |
| 2002-2004 | Rappaport Institute Research Grant - " Paraoxonases, Oxidized lipids and foam cell formation". - \$75,000. |
| 2001-2004 | Michigan Life Science Corridor Grant -“Can Paraoxonase be used to treat Endotoxemia and Sepsis?” - \$1,740,000 (PI – Dr. Bert La Du Aviram’s part - \$30,000, acting as an advisor to the University of Michigan, Department of Pharmacology Research Team.). |
| 2000-2002 | The Niedersachsische Ministeriums fur Wissenschaft and Kultur – “Role of angiotensin II in macrophage cholesterol accumulation, foam cell formation and the induction of cytokines, in the progression of atherogenesis”. – DM 200,000. |
| 1998-2000 | Rappaport Institute Research Grant - "Oxidized LDL and foam cell formation". - \$120,000. |
| 1997-2000 | The Israel Science Foundation (ISF , The Israel Academy of Sciences and Humanities) - “Coronary heart disease: genetic, environmental and behavioral determinants. - \$ 100,000 (PI - Dr. Jeremy Kark). |
| 1995-1998 | The Israel Science Foundation (The Israel Academy of Sciences and Humanities)- “Proteoglycans and macrophage uptake of oxidized LDL- \$ 150,000. |

- 1995-1997 **Rappaport Institute Research Grant** - "Oxidized LDL and foam cell formation". - \$120,000.
- 1993-1995 **Israel Ministry of Health** "Macrophage lipids peroxidation" - \$ 35,000.
- 1991-1994 **Rappaport Institute Research Grant**- "Oxidized LDL and foam cell formation". - \$ 120,000.
- 1991-1994 **German (BMFT) - Israel Binational Grant**. "Platelet secretory products and macrophage cholesterol metabolism". - DM 250,000 (Co-PI with Dr. J.G. Brook).
- 1989-1991 **Israel Ministry of Health** - "LDL-platelet interaction" - \$ 25,000.
- 1987-1988 **Fogarty International Fellowship** (Seattle, WA, USA). "Lipids - modified LDL". - \$ 40,000.
- 1984-1987 **GSF, German (BMFT) - Israel Binational Grant**. "Platelet-modified LDL". - DM 200,000 (Co-PI with Dr. J.G. Brook).
- 1983-1985 **Israel Ministry of Health** "Lipoprotein-platelet interactions" - \$ 25,000.
- 1984 **Norway - Israel Fellowship**. "Prostaglandin - lipoprotein interactions".
- 1983 **Italian - Israel Fellowship**. "Platelet prostaglandins and lipoproteins".
- 1981-1983 **Israel Ministry of Health** "Triglyceride and platelet function" - \$20,000.
- 1978-1980 **Israel Ministry of Health** "Lipoprotein abnormality in atherosclerosis" - \$20,000.

Commercial

- 2006-2008 **Ortho-Clinical Diagnostics (OCDUS) / Johnson & Johnson** – " Development of new serum paraoxonase (PON1) tests for atherosclerosis" - \$356,000 (CO-PI with Dr D. Tawfik).
- 2006-2007 **Your Energy Systems** – "Liposomal Glutathione and atherosclerosis"- \$70,000.
- 2006-2007 **Goya Holding S.A. (Genius s.r.l.)** – " Polyphenols enriched olive oil"- \$15,000.
- 1998-2008 **Roll International Ltd.** – "Nutritional antioxidants, LDL oxidation and atherosclerosis" - \$ 350,000.
- 2001-2005 **Roche Diagnostics GmbH** – "Serum paraoxonase and atherosclerosis" – DM 300,000.
- 2001-2003 **Pharmacia**– "Aldosterone, oxidative stress and atherosclerosis" - \$ 75,000.
- 1995-2001 **Lycored (Makhteshim)**- "Lycopene and LDL oxidation." \$ 180,000.
- 1998-1999 **Transphyto Ltd.** - "Dietary antioxidants and atherosclerosis" – FF 120,000.
- 1997-1998 **Dalidar Pharma Ltd.** "Ginger-derived polyphenols and atherosclerosis"- \$ 50,000.
- 1995-1997 **Sandoz Pharma AG.** - "HMGCoA reductase inhibitors". - \$ 50,000.
- 1994-1997 **Fertilizers and Chemicals** - "Licorice as an antioxidant". - \$100,000.
- 1991-1993 **Bristol-Myers Squibb Grant**. "Hypocholesterolemic therapy and lipoprotein oxidation". - \$50,000 (Co-PI with Dr. J.G. Brook).
- 1990-1992 **Merck, Sharp and Dohme Grant**. "Lipid-modified LDL and hypocholesterolemic drugs". - \$ 80,000 (Co-PI with Dr. J.G. Brook).

Technion Research grants

- 1994-present Mechanisms of lipoproteins atherogenicity- \$2500-\$5000/year.

11. CONFERENCES - International (Invited Speaker)

2006-

Aviram M. "Wine flavonoids, LDL cholesterol oxidation and atherosclerosis" The Universe of Winw and Health, March 9-12, **Firenze, Italy.**

Aviram M. "Paraonase 1 (PON1) attenuates, macrophage foam cells formation". Paraonases and oxidative stress. University of Mainz, March 13, **Mainz, Germany.**

Aviram M. "Dietary antioxidants protects against cardiovascular diseases: the pomegranate example" International Congeress on Thrombosis, May 14-16, **Tel Aviv, Israel.**

Aviram M. "Atherosclerosis, diabetes and it complications" June 7-10, **Iasi, Romania.**

Aviram M. "HDL-associated paraonase 1 (PON1) attenuates lipoprotein oxidation, macrophage foam cells formation and atherosclerosis development" International Symposium on Atherosclerosis, June 18-22, **Rome, Italy.**

Aviram M. "Paraonase and macrophage foam cell formation" Second International Conference on Paraonases, September 7-10, **Debrecen, Hungary.**

Aviram M. "Pomegranate and Cardiovascular health". 6th International Phytochemical Conference Themes and Topics Phytochemicals: Aging and Health". October 16-17, **Buena Park, CA, USA.**

Aviram M. "Antioxidant properties of olive oil against LDL oxidation and atherosclerosis development". 28th ESPEN Congress Clinical Nutrition and Metabolism. Octorber 19-22, **Istanbul, Turkey.**

Aviram M. "Naturitional antioxidants protect against atherosclerosis: role for HDL-associated paraonase" Fourth international conference on mechanisms of action of nutraceuticals (ICMAN 4), October 29- November 1, **Tel –Aviv, Israel.**

Aviram M. "Dietary antioxidants and paraonase attenuate macrophage foam cell formation and atherosclerosis development" Nutrition, Lipids and Atherosclerosis. November 17-18, **Madrid, Spain.**

2005-

Aviram M. "Dietary tomatoe's lycopene reduces heart diseases" International Conference on Antioxidant and Lycopene, March 16, **London.**

Aviram M. "Macrophage NADPH oxidase and foam cell formation: Anti-atherosclerotic role for dietary antioxidants and for paraonase", Workshop on "new insights in mechanisms of vascular diseases", May 20-21, **Baveno, Maggiore Lake, Italy.**

Aviram M. "Oxidative stress and cardiovascular diseases: protective role of dietary antioxidants". Visual Function – Insights from the revolution in biology at the molecular level". June 14-16,

Tel Aviv, Israel.

Aviram M. and Fuhrman B. "Pomegranate and CVD: pomegranate juice polyphenolic antioxidants protect against oxidative stress and atherosclerosis development", Symposium on Human Health effect of Fruits and Vegetables, August 18-20, **Quebec City, Canada.**

2004-

Aviram M. "Paraoxonases protective mechanisms against oxidative stress, macrophage foam cell formation and atherosclerosis development". The 74th EAS Congress. April 17-20, **Seville, Spain** (Speaker and Organizer).

Aviram M. "Paraoxonase (PON1) protects against lipids peroxidation and attenuates atherosclerosis development". The First International Meeting on Paraoxonases – Basic and Clinical Directions of Current Research. April 23-24, **Ann Arbor, MI, USA** (Speaker and Organizer).

Aviram M. "HDL-associated paraoxonase1 (PON1) antioxidant and anti-inflammatory properties: PON1 protection against macrophage foam cell formation and atherosclerosis development". September 2-6, HDL Workshop. **Heraklion, Crete, Greece.**

Aviram M. "Paraoxonases and macrophage foam cells formation". Frontiers in Cardiovascular Science, October 14-17, **Eilat, Israel.**

Aviram M. "Paraoxonases and diabetes". The Russell Berrie 1st international Diabetes Symposium. October 17-19, **Jerusalem, Israel.**

Aviram M. "Dietary antioxidants and paraoxonases: protection against cardiovascular diseases". International Conference on Mechanisms of action of Nutraceuticals (ICMAN). November 12-14, **Waynsville, Haywood County, Western North Carolina, U.S.A.** (Speaker and Organizer).

2003-

Aviram M. "Mediterranean dietary antioxidants inhibit macrophage foam cell formation". September 20-23, **Cannes, France** (Speaker and Organizer).

Aviram M. "Molecular pharmacology of herbal medicine and botanical products in the treatment of vascular disease: the pomegranate example". Traditional herb medicines in Atherosclerosis Symposium. September 24-27, **Taipei, Taiwan.**

Aviram M. "Flavonoids-rich nutrients with potent antioxidant activity prevent atherosclerosis development". The XIIIth International Symposium on Atherosclerosis. September 28- October 2, **Kyoto, Japan** (Speaker and Organizer).

Aviram M. "Paraoxonases protects against oxidative stress and atherosclerosis progression at the humoral and cellular levels". Frontiers in Cardiovascular Science, October 23-26, **Eilat** (Speaker and Organizer).

2002-

Aviram M. "Oxysterols induce macrophage NADPH oxidase activation". XIth Biennial Meeting of the Society for Free Radical Research International: Role of free radicals, oxidants and antioxidants, in molecular and cell biology and life processes: New developments and techniques". July 16-20, **Paris, France.**

Aviram M. 1st Plenary Meeting, EC Concerted Action on Process for the Assessment of Scientific Support for Claims on Foods – PASSCLAIM. September 4-6, **Berlin, Germany**(Advisory Board member).

Aviram M. "Paraoxonase and Atherosclerosis". XIII Lipid-Meeting, Leipzig", September 30th – October 2nd, **Leipzig, Germany.**

Aviram M. "Paraoxonase protects against oxidative stress and atherosclerosis progression". Frontiers in Cardiovascular Science, October 3-6, **Eilat** (Speaker and Organizer).

Aviram M. "Oxidative stress, macrophage foam cell formation and Atherosclerosis". European Community Center of Excellence Workshop on: "Cardiovascular dysfunctions in hyperlipidemia and diabetes". October 9-13, **Bucharest, Romania.**

Aviram M. "Wine flavonoid antioxidant against LDL oxidation". Vinsalude 2002 Chile: Wine and Health International Congress, October 20-23, **Santiago, Chile** (Speaker and Organizer).

Aviram M. "Macrophage, Foam Cell formation and Atherosclerosis under Oxidative Stress: studies in the apolipoprotein E deficient mice". Biocenter Oulu Graduate School Advance Course: From cells to tissues: signaling and mechanisms, December 3, **Oulu, Finland.**

2001-

Aviram M. "New Avenues in Atherosclerosis Research: Genomics and New Therapeutical Perspectives". March 14-15, **Montreal, Canada.**

Aviram M. "Wine polyphenols, LDL oxidation and atherosclerosis", "Conference on Wine and Alcohol in Health and Disease". April 26-29, **Palo Alto, California, USA.**

Aviram M. "Dietary antioxidants and cardiovascular diseases" International Conference on Mechanisms of action of Nutraceuticals (ICMAN). October 10-14, **Dubrovnik, Croatia.**

2000-

Aviram M. "Anti-atherogenicity of the licorice derived isoflavane glabiridin: inhibitory role in LDL oxidation and macrophage foam cell formation". The Oxygen Club of California, 2000 orld Congress, March 1-4, **Santa Barbara, California, USA.**

Aviram M. "Role of angiotensin II in lipoprotein oxidation and cholesterol metabolism in the vascular wall". The 15th American Society of Hypertension (ASH) meeting. May 15-19, **New York, NY, USA.**

Aviram M. "Polyphenols inhibit LDL Oxidation and Atherosclerosis". XXth International Conference on Polyphenols, September 11-15, **Freising, Germany.**

Aviram M. "Antioxidant activity of statins as well as of pomegranate juice", PTBNM Polish society for atherosclerosis research MEM, October, 23-26 in **Krag Castle, Koszalin, Poland.**

1999-

Aviram M. "Paraoxonase, LDL Oxidation and Macrophage Foam Cell Formation". The 2nd Rappaport – Mayo Symposium on vascular biology: therapeutic horizons in cardiovascular disease. May 23-27, **Rochester, MN, USA.**

Aviram M. "Review of Human Studies related to vascular function". ILSI Europe Workshop on Markers of Oxidative Damage and Antioxidant protection. June, 28-30, **Prague, Czech Republic.**

Aviram M. "Functional Ingredients in Wine". 4th Karlsruhe Nutrition Symposium on Vegetables and Fruit for better Nutrition and Health: Scientific evidence and Practical Experiences. October, 10-12, **Karlsruhe, Germany.**

Aviram M. "Oxidized LDL and Atherosclerosis: Role of Antioxidants and Paraoxonase" 10th International Dresden Symposium on Lipoproteins and Atherosclerosis. December, 9-11, **Dresden, Germany.**

1998-

Aviram M. "LDL oxidation in athpatients and the effect of drug therapy". The Pfizer Lecture, February 9, **Montreal, Canada.**

Aviram M. "LDL oxidation and atherosclerosis: antiatherogenicity of antioxidants". The first regional meeting on medical science-The roles of free radicals in health and disease" March 22-27, **Jerusalem-Amman, Israel-Jordan (Speaker and Organizer).**

Aviram M. "Anti-atherogenicity of antioxidants against LDL oxidation" The Second International Conference on Natural Antioxidants and Anticarcinogens in Nutrition, Health and Disease (NAHD). June 24-27, **Helsinki, Finland.**

Aviram M. "Tomato's lycopene and β -carotene inhibit LDL oxidation. Nutracon, July 20-22, **San Antonio, Texas.**

Aviram M. "Paraoxonase reduces lipoprotein oxidation: a possible role for its per-like activity". The European Atherosclerosis Society, 70 EAS Meeting, September 6-9, **Geneva, Switzerland.**

Aviram M. "Human serum paraoxonase, lipoprotein oxidation and atherosclerosis". The 5th International Union of Biochemistry and Molecular Biology (IUBMB) Conference on the Biochemistry of Health and Diseases. October, 18-22, **Jerusalem, Israel.**

Aviram M. "Dietary antioxidants against LDL oxidation in cardiovascular diseases". American College for advancement in Medicine, November 20-22, **Phoenix, Arizona.**

1997-

Aviram M. "Macrophage-mediated oxidation of LDL" - The first joint meeting of the Rappaport Institute and the University of Dundee. January 26-28, **Dundee, Scotland, U.K.**

Aviram M. "LDL oxidation by macrophages". The first international workshop on molecular biology of mononuclear phagocyte differentiation and activation. **Advisory Board Expert.** May 2-3, **Regensburg, Germany.**

Aviram M. "Inhibition of LDL oxidation by macrophage - and by LDL - associated antioxidants" - The 68th meeting of the European Atherosclerosis Society (EAS): Molecular Cell Biology and Atherosclerosis. May 7-10, **Brugge, Belgium.**

Aviram M. "Antiatherogenicity of statin therapy in hypercholesterolemic patients: effects on platelet activation and on LDL oxidation". The 29th annual meeting of Japan Atherosclerosis Society (JAS). June 5-6, **Tokyo, Japan.**

Aviram M. "Dietary antioxidants and LDL oxidation". The 2nd world conference of the international society for molecular nutrition and therapy. August 2-4, **Winnipeg, Canada.**

Aviram M. "Lipoprotein oxidation and atherosclerosis"- **Chairman of the workshop.** 11th International Symposium on Atherosclerosis. October 5-9, **Paris, France.**

Aviram M. "Macrophage-mediated oxidation of LDL and atherosclerosis". The First Rappaport-Mayo Symposium on Vascular Biology. December 1, **Haifa, Israel.**

1996-

Aviram M. "Role of oxidized LDL in the development of atherosclerosis". The Menarini Series on Cardiovascular Diseases: Advances in Cardiovascular Pathology. January 26-27, **Florence, Italy.**

Aviram M. "Antioxidants against LDL oxidation and Atherosclerosis". March 1st, **Naarden, The Netherlands.**

Aviram M. "Lycopene and Atherosclerosis". BioMed, Inaugural Lecture Program, March 2nd, **Birmingham, U.K.**

Aviram M. "Interrelationship among platelet activation, LDL oxidation and foam cell formation in hypercholesterolemic patients: antiatherogenic effects of statin therapy". Asian-Pacific Congress on Vascular Diseases. March 11-15, **Singapore.**

Aviram M. "Macrophage relevance in the atherome plaque formation. Effects of pravastatin in the inhibition of cellular cholesterol synthesis and increase of LDL receptor activity in macrophages". International Symposium on Coronary Prevention and Lipidic Control: Fisiopathologic basis and new Therapeutic Consensus. Laboratories Dr. Esteve. S.A., April 19-20, **Barcelona, Spain.**

Aviram M. "Oxidative modification of LDL and Atherosclerosis". V Simposio International Sorbe, Alimentation, Lipidos Y Atherosclerosis. May 30- June 1, **Madrid, Spain.**

Aviram M. "Macrophage-mediated oxidation of LDL depends on the balance between cellular oxygenases and antioxidants". 66th Congress of the European Atherosclerosis Society, July 13-17, **Florence, Italy.**

Aviram M. "Interrelationship among platelet activation, LDL oxidation and foam cell formation in hypercholesterolemic patients: antiatherogenic effects of statin therapy" 66th Congress of the European Atherosclerosis Society, July 13-17, **Florence, Italy.**

Aviram M. "LDL enrichment with tomato's lycopene increases its resistance to oxidation in the atherosclerotic, apolipoprotein E deficient transgenic mice" 11th International symposium on Carotenoids. August 18-23, **Leiden, The Netherlands.**

Aviram M. "Macrophage-mediated oxidation of LDL: role of cellular-and lipoprotein-associated antioxidants". 2nd International Conference on Lipoprotein Oxidation and Atherosclerosis: Biological and Clinical Aspects. September, 12-14, **Pavia, Italy.**

Aviram M. "Inhibition of LDL oxidation by macrophage-and LDL-associated antioxidants". **Chairman of the Symposium.** International Symposium on vitamins and antiproliferative agents in prevention of atherosclerosis. The 4th Congress of the Polish Society for Atherosclerosis Research. October 3-6, **Zokopane, Poland.**

Aviram M. "Red wine quercetin inhibits LDL oxidation and aggregation in the atherosclerotic, apolipoprotein E deficient, transgenic mice". The First Workshop on Wine and Human Health. October 9-11, **Udine, Italy.**

Aviram M. "Macrophage proteoglycans contribute to the binding and uptake of oxidized low density lipoprotein (Ox-LDL). The 69th Scientific Sessions, American Heart Association (AHA), November 10-13, **New Orleans, Louisiana, U.S.A.**

1995-

Aviram M. "Macrophage uptake of oxidized LDL inhibits lysosomal sphingomyelinase, thus causing the accumulation of unesterified cholesterol". 5th Rappaport Symposium:

Modified Lipoproteins, Antioxidants and Atherosclerosis. **Chairman of the Symposium.**
May, 8-12, **Shavei Zion, Israel.**

Aviram M. "Oxidative stress affects LDL-platelet interactions and induce foam cell formation".
XVth Congress of the International Society on Thrombosis and Haemostasis. June 11-16,
Jerusalem, **Israel.**

Aviram M. "Platelet activation, LDL oxidation and foam cell formation". 1st International Meeting
on Interventional Cardiology. June 18-23, **Jerusalem, Israel.**

Aviram M. "Platelets and macrophage cholesterol accumulation". 11th IFCC European Congress
of Clinical Chemistry. July 2-7, **Tampere, Finland.**

Aviram M. "Oxidized LDL and macrophage accumulation of unesterified cholesterol".
Third Scientific Meeting of the Polish Society for Atherosclerosis Research. October 5-8,
1995, **Cracow, Poland.**

Aviram M. "Dietary Antioxidants against LDL oxidation and atherosclerosis". Annual Meeting
of the Indian Society for Atherosclerosis Research. December 8-10. **New Delhi, India.**

Aviram M. "Inhibition of LDL oxidation by carotenoids: a comparative study of lycopene
and β -carotene". International Conference of Food Factors. December, 10-15. **Hamamatsu, Japan.**

1994-

Aviram M. "Macrophage-mediated modification of LDL and atherosclerosis".
IV International Symposium on Lipids and Atherosclerosis. May 5-7. **Madrid, Spain.**

Aviram M. "Oxidized LDL and Atherosclerosis". Senior Investigator Arcol Prize laureate.
Hundred years celebration to Pasteur Institute. June 2-4. **Lille, France.**

Aviram M. "LDL lipid modifications increases its Atherogenicity". Second Congress of the
Polish Society for Atherosclerosis Research. June 4-7. **Szczecin, Poland.**

Aviram M. "phospholipase-modified LDL and Atherogenesis". 8th International Dresden
Lipid Symposium. June 10-12. **Dresden, Germany.**

Aviram M. "Macrophage-mediated Oxidation of LDL and Atherosclerosis". Society for Free
Radical Research. September 16-18. **Pavia, Italy.**

1993-

Aviram M. "Dietary olive oil decrease LDL atherogenicity. The VII Creteil Symposium on
Nutrition, Lipids and Lipoproteins". February 12. **Paris, France.**

Aviram M. "Beyond cholesterol: Modification of lipoproteins and increased atherogenicity". International symposium on Atherosclerosis, Inflammation and Thrombosis". March 21-24, **Florence, Italy.**

Aviram M. and Rosenblat M. "Macrophage-mediated oxidamodification of LDL". Joint Meeting of the German and Societies for Cell Biology (DGX and NVVC), March 28-31. **Munster, Germany.**

Aviram M. "LDL lipids modifications and increased atherogenicity". 62nd European atherosclerosis Society. September 5-9. **Jerusalem, Israel.**

Aviram M. "Antioxidant mediated inhibition of LDL-modifications reduces its atherogenicity". International SFRR symposium on Antioxidants, Inflammation, Cardiovascular and Ophthalmic disease. Servier Award. September 30 - October 2. **Valencia, Spain.**

1992-

Aviram M. "Serotonin increased macrophage uptake of oxidized low density lipoprotein". XI International Symposium on Drugs affecting Lipid Metabolism, May 13-16. **Florence, Italy.**

Aviram M. "Increased susceptibility to activation and increased uptake of low density lipoprotein by choleloaded macrophages". 59 European Atherosclerosis Society Congress. May 17-21. **Nice, France.**

Aviram M. "Lipids and platelet function in the development of atherosclerosis in diabetes". The Second International Symposium on Diabetes and Atherosclerosis, September 5-7. **Carlsbad, Czechoslovakia.**

Aviram M. "Macrophage-mediated LDL oxidation required LDL binding to the LDL receptor". 33rd International conference on the Biochemistry of Lipids (ICBL). September 7-10. **Lyon, France.**

Aviram M. "Phospholipase D-modified low-density lipoprotein is taken up by macrophages at an increased rate: A possible role for phosphatidic acid". 65th Scientific Sessions, American Heart Association (AHA), November 16-19. **New Orleans, LA, U.S.A.**

1991-

Aviram M. "Platelet mediated cholesterol accumulation in macrophages". 9th International Symposium on Atherosclerosis. October 6-11. **Chicago, (Rosemont) IL, U.S.A.**

1990-

Aviram M. "Platelet enhancement of macrophage cholesterol accumulation: a novel mechanism

for atherogenesis". 2nd Mediterranean Congress of Angiology. September 16-22.
Antalya, Turkey.

Aviram M. "Platelet enhancement of macrophage cholesterol accumulation: A novel mechanism for atherogenesis". European Lipoprotein Club Meeting. September 17-20.
Tutzing, Germany.

Aviram M. "Platelet enhancement of macrophage cholesterol accumulation: A novel mechanism for atherogenesis". 63rd Scientific Sessions, American Heart Association. November 12, 1990, **Dallas, TX, U.S.A.**

1989-

Aviram M. "Lipase modified LDL and macrophage cholesterol accumulation". International Meeting on atherosclerosis (EAS). April 20-22. **Wien, Austria.**

Aviram M. "Macrophage uptake of oxidized LDL is increased by platelet secretory products". European Lipoprotein Meeting September 11-14. **Tutzing, Germany.**

Aviram M. "Lovastatin inhibits LDL oxidation". International symposium on drugs affecting lipid metabolism. November 8-11. **Houston, TX, U.S.A.**

Aviram M. "Macrophage uptake of oxidized LDL is increased by platelet secretory products". 62nd Scientific Sessions of the American Heart Association. November 13-16. **New Orleans, LA, U.S.A.**

1988-

Aviram M. "Lipase-modified LDL results in cholesterol accumulation in macrophages". American Federation for Clinical Research (AFCR), Western Section. February 16-19. **Carmel, CA, U.S.A.**

Aviram M. "Low density lipoprotein triglyceride content determines its interaction with cells". 8th International Symposium on Atherosclerosis. October 9-13. **Rome, Italy.**

Aviram M. "Triglyceride content of LDL affects the interaction of apo B with cells". 61st Scientific Sessions, American Heart Association, November. **Washington, D.C., U.S.A.**

1987-

Aviram M. "Intralipid infusion abolishes the ability of human serum to cholesterol load cultured macrophages". 60th Scientific Sessions, American Heart Association. November 16-19. **Anaheim, CA, U.S.A.**

1985-

Aviram M. "Antithrombotic effect of plasma chylomicrons on endothelial cells: differences between dietary cream and cod liver oil". Seventh International Symposium on Atherosclerosis. October 6-10. **Melbourne, Australia.**

1984-

Aviram M. "Chylomicron atherogenicity: Plasma chylomicrons decrease platelet function". Seventh Annual Conference on Lipoproteins. The European Lipoprotein Club. September 10-13. **Tutzing, Germany.**

1980-

Aviram M. "Low-density lipoprotein receptors on human platelets". American Federation for Clinical Research (AFCR). February 10-15. **Washington D.C. U.S.A.**

PUBLICATIONS

Theses

1. M.Sc. thesis: "Energy requirement of the intracellular breakdown of ribonucleic acid".
2. D.Sc. thesis: "Turnover of tyrosine-aminotransferase in hepatoma tissue culture cells".

Refereed Papers in Professional Journals

1. Tal M., **M. Aviram**, A. Kanarek, and A. Weiss. Polyuridylic acid binding and translating by *Escherichia coli* ribosomes: stimulation by protein I, inhibition by aurointricarboxylic acid. *Biochim Biophys Acta* **281**: 381-392 (1972).
2. **Aviram M.**, and A. Hershko. Influence of ATP on the degradation of rapidly labeled RNA in cultured hepatoma cells. *Biochem Biophys Res Commun* **65**: 1303-1310 (1975).
3. **Aviram M.**, and A. Hershko. Interconversion of multiple forms of tyrosine-aminotransferase in vitro and in vivo in cultured hepatoma cells. *Biochim Biophys Acta* **498**: 83-90 (1977).
4. Rapoport J., **M. Aviram**, C. Chaimovitz, and J.G. Brook. Defective high-density lipoproteins composition in patients on chronic hemodialysis. A possible mechanism for accelerated atherosclerosis. *N Engl J Med* **299**: 1326-1329 (1978).
5. Brook J.G., A. Lavy, **M. Aviram**, and O. Zinder. The concentration of high-density lipoprotein in patients with type IV hyperlipoproteinemia and the effect of clofibrate. *Atherosclerosis* **36**: 461-469 (1980).
6. **Aviram M.**, J.G. Brook, A.M. Lees, and R. S. Lees. Low density lipoprotein binding to human platelets: role of charge and of specific amino acids. *Biochem Biophys Res Commun* **99**: 308-318 (1981).
7. Brook J.G., **M. Aviram**, R. Luboshitzky and D. Barzilai. High density lipoprotein and arteriosclerosis. Different patterns in primary hypothyroidism and type IIa hyperlipoproteinemia. *Isr J Med Sci* **17**: 318-322 (1981).
8. **Aviram M.**, and J.G. Brook. The effect of human plasma on platelet function in familial hypercholesterolemia. *Thromb Res* **26**: 101-109 (1982).

9. Brook J.G., **M. Aviram**, A. Viener, E. Shilansky, and W. Markiewicz. High-density lipoprotein subfractions in normolipidemic patients with coronary atherosclerosis. *Circulation* **66**: 923-926 (1982).
10. **Aviram M.**, R. Luboshitzky, and J.G. Brook. Lipid and lipoprotein pattern in thyroid dysfunction and the effect of therapy. *Clin Biochem* **15**: 62-66 (1982).
11. **Aviram M.**, Z. Blumenfeld, J.G. Brook, A. Levy and J. Brandes. High-density lipoprotein and its subfractions in cord blood. *Singapore J Obstet Gynecol* **13**: 107-114 (1982).
12. **Aviram M.**, J.G. Brook, S. Mokady, R. Diukman, B. Fogel and U. Cogan. Changes in rabbits' plasma lipoprotein pattern induced by substituting soybean protein for dietary animal protein. *Nutr Rep Intern* **26**: 569-579 (1982).
13. Brook J.G., **M. Aviram**, M. Oettinger and M. Sharf. The effect of estrogen implants on high density lipoproteins and its subfractions in women in their early pre-mature menopause. *Maturitas* **4**: 257- 265 (1982).
14. Ron D., I. Oren, **M. Aviram** ,O.S.Better, and J.G. Brook. Accumulation of lipoprotein remnants particles in patients with chronic renal failure. *Atherosclerosis* **46**: 67-75 (1983).
15. **Aviram M.**, and J.G. Brook. Platelet interaction with high and low-density lipoproteins. *Atherosclerosis* **46**: 259-268 (1983).
16. Brook J.G., G. Winterstein, and **M. Aviram**. Platelet function and lipoprotein levels after plasma-exchange in patients with familial hypercholesterolemia. *Clin Sci* **64**: 637-642 (1983).
17. **Aviram M.** Plasma lipoprotein separation by discontinuous density gradient ultracentrifugation in hyperlipoproteinemic patients. *Biochem Med* **30**:111-118 (1983).
18. Blumenfeld Z., **M. Aviram**, J.G. Brook, and J.M. Brandes. Changes in lipoprotein and subfractions following oophorectomy and oestrogen replacement in perimenopausal women. *Maturitas* **5**:77-84 (1983).
19. **Aviram M.**, and J.G. Brook. The effect of blood constituents on platelet function: role of blood cells and plasma lipoproteins. *Artery* **11**: 297-305 (1983).
20. Ron D., **M. Aviram**, and J.G. Brook. High density lipoprotein in octogenarians. *Biochem Med* **30**:253-260 (1983).
21. Markel A., J.G. Brook, Y. Levy, **M. Aviram**, and M.B.H. Youdim. Increased platelet adhesion and aggregation in hypertensive patients: effect of atenolol. *Br J Clin Pharmacol* **16**:663-668 (1983).
22. **Aviram M.**, and J.G. Brook. Characterization of the effect of plasma lipoproteins on platelet function in vitro. *Haemostasis* **13**:344-350 (1983).

23. Mokady S., U.Cogan, G. Dreifus, **M. Aviram** and J.G. Brook. Plasma lipids and lipoproteins in normo-and hyperlipidemic rabbits fed plant protein diets. *Nutr Res* **4**:897-902 (1984).
24. Baruch Y., J.G. Brook, S. Eidelman, and **M. Aviram**. Increased concentration of high density lipoprotein plasma and decreased platelet aggregation in primary biliary cirrhosis. *Atherosclerosis* **53**:151- 162 (1984).
25. Viener A., J.G. Brook, and **M. Aviram**. Abnormal plasma lipoprotein composition in hypercholesterolemic patients induces platelet activation. *Eur J Clin invest* **14**: 207-213 (1984).
26. Shmulewitz A., J.G. Brook, and **M. Aviram**. Native and modified low-density-lipoprotein interaction with human platelets in normal and homozygous familial-hypercholesterolemic subjects. *Biochem J* **224**: 13-20 (1984).
27. **Aviram M.**, and J.G. Brook. Selective release from platelet granules induced by plasma lipoproteins. *Biochem Med* **32**: 30-33 (1984).
28. Levy Y., **M. Aviram**, G. Spira, I. Tatarsky, J.G. Brook, and A. Carter. Plasma cholesterol concentration and extra lipid band in monoclonal gammopathies. *Postgrad Med J* **60**:449-453 (1984).
29. Haim S., J.G. Brook, A. Gilhar, R. Friedman-Birnbaum, A. Markel, **M. Aviram**, A. Marmur, and M.B.H. Youdim. Platelet function in Behcet's disease. *J Dermatol* **11**:117-120 (1984).
30. Weschler A., **M. Aviram**, M. Levin, O.S. Better, and J.G. Brook. High dose of L-carnitine increases platelet aggregation and plasma triglyceride levels in uremic patients on hemodialysis. *Nephron* **38**: 120-124 (1984).
31. Berkovitch Y., A. Marmur, J.G. Brook, and **M. Aviram**. Platelet adhesion determination in whole blood using a simple stagnation flow method. *Ann Biomed Eng* **12**:335-346 (1984).
32. **Aviram M.**, B. Fuhrman, and J.G. Brook. Chylomicrons from patients with type V hyperlipoproteinemia inhibit platelet function. *Atherosclerosis* **56**: 157-167 (1985).
33. **Aviram M.**, G. Winterstein, and J.G. Brook. Differential effect of platelet inhibitors in normal and in hypercholesterolemic subjects. *Br J Clin Pharmacol* **19**: 715-719 (1985).
34. **Aviram M.**, R.J. Deckelbaum, and J.G. Brook. Platelet function in a case with abetalipoproteinemia. *Atherosclerosis* **57**:313-323 (1985).
35. Markel A., J.G. Brook, and **M. Aviram**. Increased plasma triglycerides, cholesterol and apolipoprotein E during prolonged fasting in normal subjects. *Postgrad Med J* **61**:395-400 (1985).

36. Marmur A., E. Braunstein, J.G. Brook, and **M. Aviram**. Sedimentation and adhesion of blood platelets under centrifugal force. *J Colloid Interface Sci* **104**: 390-397 (1985).
37. **Aviram M.**, Y. Schechter, and J.G. Brook. Chylomicron-like particles in severe hypertriglyceridemia. *Lipids* **20**: 211-215 (1985).
38. **Aviram M.**, C.R. Sirtori, S. Colli, P. Maderna, G. Morazzoni, and E. Tremoli. Plasma lipoproteins affect platelet malondialdehyde and thromboxane B2 production. *Biochem Med* **34**:29-36 (1985).
39. **Aviram M.**, A. Carter, J.G. Brook, and I. Tatarsky. Chylomicronaemia in multiple myeloma. *Scand J Haematol* **34**: 436-441 (1985).
40. **Aviram M.**, A. Carter, I. Tatarsky, Y. Levy, and J.G. Brook. Increased platelet aggregation following splenectomy in patients with myeloproliferative disease. *Isr J Med Sci* **21**:415-417(1985).
41. Lorber M., **M. Aviram**, S. Linn, Y. Scharf, and J.G. Brook. Hypocholesterolemia and abnormal high-density lipoprotein in rheumatoid arthritis. *Br J Rheumatol* **24**:250-255 (1985).
42. **Aviram M.**, and J.G. Brook. Plasma lipoprotein pattern and decreased platelet function in type V hyperlipoproteinemia. *Isr J Med Sci* **21**:898-904 (1985).
43. Brook J.G., A. Marmur, Y. Berkovitz, and **M. Aviram**. Platelet adhesion in hyperlipidemic and hypertensive patients. *Haemostasis* **15**:371-376 (1985).
44. Manaster J., **M. Aviram**, I. Silvian, J. Chezar, and G. Spira. Serum immunoglobulin - lipid complexes in plasma cell dyscrasia. *Scand J Immunol* **22**:425-431 (1985).
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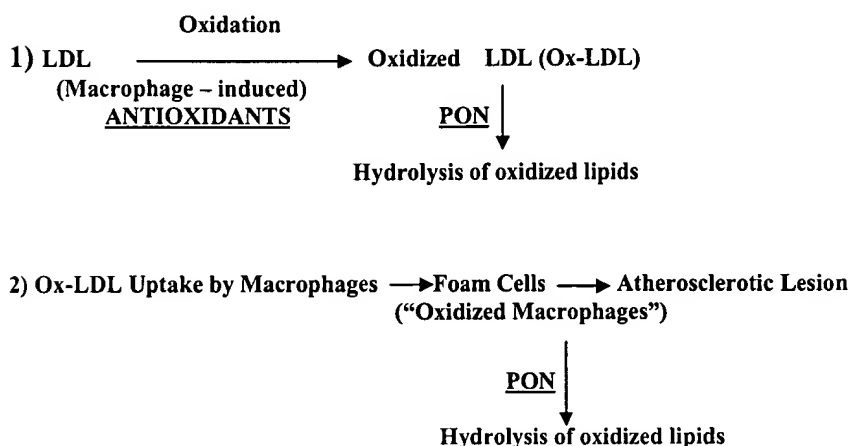
Appendix

Research Accomplishments

Michael Aviram

Broad Objective

Macrophage Cholesterol accumulation and Foam Cell formation under Oxidative Stress during Atherogenesis: Role of Dietary Antioxidants and of Paraoxonase.



Specific Research Areas

1. Lipoproteins Oxidation and Atherosclerosis (1980 – present)

Oxidative stress is thought to play a key role in the development of atherosclerosis, the major cause of morbidity and mortality in the western world. We have shown that LDL oxidation, as well as additional **lipoprotein modifications** contribute to enhanced atherogenicity of LDL (1-5). Studies on mechanisms of **oxidized LDL (Ox-LDL) retention to extracellular matrix (ECM) proteoglycans** (heparan and chondroitin sulfate), as related to the lipoprotein uptake by macrophages scavenger receptors, leading to cellular accumulation of cholesterol and oxysterols, are carried out in our laboratory (6-9). **Macrophage – mediated oxidation of LDL** and foam cell formation is the hallmark of early atherogenesis, and we have demonstrated the role of cellular oxygenases (such as NADPH oxidase) and of antioxidants (such as the glutathione

system) in macrophages, as well as in LDL oxidation. We have demonstrated that under oxidative stress, not only the lipoproteins are oxidized, but also the cellular lipids. We showed the presence of Ox-LDL and of **lipid peroxidized macrophages** in the atherosclerotic lesion, and demonstrated that these oxidized cells are able to oxidize LDL even in the absence of transition metal ions (10-12). We have shown **increased LDL oxidation in patients** with increased risk for atherosclerosis (hypercholesterolemia, hypertension, diabetes, chronic renal failure). Drug therapy in these patients (hypocholesterolemic “statins”, ACE inhibitors) reduced the patient’s increased LDL oxidation (13-14).

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2. Dietary Antioxidants and Atherosclerosis (1990 – present)

Dietary antioxidants that inhibit LDL oxidation can attenuate atherosclerosis development , and we have demonstrated indeed such properties for vitamin E, carotenoids (lycopene, β -carotene), and mainly for polyphenolic flavonoids, such as those found in pomegranate (hydrolyzable tannins), wine (flavonols), licorice (isoflavans) , ginger (flavonones) and olive oil (phenolics).

We have provided evidence that the inhibitory effect of some flavonoids on LDL oxidation (and on atherosclerosis) is related to their interaction with the lipoprotein directly, as well as to their accumulation in arterial macrophages and inhibition of cellular oxygenases (1-9).

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3. Paraoxonase ,Lipids Peroxidation and Atherosclerosis (1997 – present)

Under excess oxidative stress, antioxidants capability to block the formation of Ox-LDL may not be sufficient. We have recently demonstrated that HDL - associated **Paraoxonase** (PON1) can hydrolyze oxidized lipids (such as cholesteryl linoleate hydroperoxides) in oxidized lipoproteins and in atherosclerotic lesion, and thus may act as a second line of defense against oxidative stress. Combination of potent antioxidants (flavonoids) together with paraoxonase was shown in our laboratory to attenuate atherogenesis, secondary to reduced oxidative stress and reduce macrophage uptake of oxidized lipoproteins via the scavenger receptors (1-14).

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